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From : Barry S. Wilson
Date : October 10, 2004
Client/Matter No : 088802-2753
User ID No : 3067

MESSAGE: Re: U.S. Patent Application No. 09/515,276
Our Ref.: SALK1650-2 (088802-2753)

Attached please find:

- Transmittal (1 pg.);
- Reply to Examiner's Answer Under 37 C.F.R. §41.41 (8 pages);
- Copy of The Regents of the University of California v. Eli Lilly and Company (Fed. Cir. 1997) (12 pages);
- Copy of University of Rochester v. G.D. Searle & Co. (Fed. Cir. 2004) (16 pages).
- Authorization to charge Deposit Acct. No. 50-0872 any fees due.

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PATENT
Atty. Docket No. SALK1650-2
(088802-2753)

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Applicant: Marc R. Montminy

Title: METHODS FOR TREATING DIABETES MELLITUS

Appl. No.: 09/515,276

Filing Date: 02/29/2000

Examiner: D. Wortman

Art Unit: 1648

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Sir:

Enclosed please find the following:

[X] Reply to Examiner's Answer Under 37 C.F.R. §41.41 (8 pages).

[X] Copy of The Regents of the University of California v. Eli Lilly and Company (Fed. Cir. 1997) (12 pages).

[X] Copy of University of Rochester v. G.D. Searle & Co. (Fed. Cir. 2004) (16 pages).

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Respectfully submitted,

Date: October 11, 2004

By _____

Barry S. Wilson
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PATENT
Atty. Docket No. SALK1650-2
(088802-2753)

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Applicant:	Marc R. Montminy
Title:	METHODS FOR TREATING DIABETES MELLITUS
Appl. No.:	09/515,276
Filing Date:	02/29/2000
Examiner:	D. Wortman
Art Unit:	1648

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REPLY TO EXAMINER'S ANSWER UNDER 37 CFR § 41.41

Mail Stop APPEAL BRIEF - PATENTS
Commissioner for Patents
PO Box 1450
Alexandria, Virginia 22313-1450

Sir:

Appellant submits this Reply in response to the Examiner's Answer mailed August 12, 2004. No fee is believed due for this Reply, however, if this is incorrect and additional fees are due in this regard, please charge or credit Deposit Account No. 50-0872 for the appropriate amount.

The Examiner's Answer indicates abandonment of numerous positions taken by the Examiner in the Final Office Action. What remains is a written description rejection based on an assertion of law that extends well beyond anything ever addressed by the Federal Circuit and an enablement rejection which is founded on an out-of-context reading of the word "may." These points are highlighted in greater detail below.

Enablement rejection

1. The Mayr et al. and Herzig et al. references do not support the enablement rejection

It is respectfully submitted that the rejection for lack of enablement rests entirely on the alleged unpredictability in the art as allegedly demonstrated by the Mayr et al. and Herzig et al. publications. Examiner's Answer, p.9-10. The only support in these references for the Examiner's position is the use of the word "may" in three sentences at the end of the Herzig et al. reference.

> The effect of A-CREB on liver gene expression suggests that CREB **may** constitute a ideal target for therapeutic intervention. Although use of dominant negative inhibitor such as A-CREB may not be feasible in this regard, small molecules that block CREB phosphorylation or disrupt recruitment of the CREB coactivator CBP (CREB binding protein) **may** prove effective. Such compounds **may** be particularly beneficial as adjunctive therapy in lowering fasting blood glucose levels in early type II diabetes.

Herzig et al., p. 182 (emphasis as used in Office Action). However, when read in the proper context of very lofty goals i.e., "may constitute an ideal target or "may be particularly beneficial" (emphasis added), the cited text hardly supports a view that the field is unpredictable. Furthermore, this alleged unpredictably premised on the use of the word "may" is at odds with the rest of the Herzig et al. reference and the Mayr et al. reference when viewed as a whole.

Both references support predictability of the field by demonstrating the key principle underlying Appellant's approach to diabetes mellitus treatment. Mayr et al. describes the mechanism by which CREB controls glucose homeostasis, involving phosphorylation of CREB at Ser133, which promotes complexing with the transcriptional co-activator CBP. Mayr et al., p599, left column and Figure 1a. The Abstract of Mayr et al. states that CREB "functions in glucose homeostasis." These conclusions are consistent with Appellant's disclosure teaching involvement of CREB-CBP complex in diabetes. Viewed in this light, it is respectfully submitted that one skilled in the art would view the Mayr et al. reference as imparting a positive rather than a negative outlook. Furthermore, Herzig et al. reports that CREB controls glucose homeostasis through expression of gluconeogenic enzymes via the transactivator, PGC-1. Herzig et al. also used normal and diabetic animals to prove that a reduced CREB activity causes fasting hyperglycemia in vivo, a result that Herzig states "is correlated with Type II diabetes." Herzig et al., page 179 (Abstract).

In sum, these two references demonstrate predictability in the field through a validation of the goals of the claimed invention. In contrast, the evidentiary support underpinning the

enablement rejection is limited to the word "may," which then must be read out of context and even then does not comport with the references when taken as a whole.

2. The Examiner is incorrect that Appellants have not demonstrated that inhibition of CREB/CBP occurs with the inhibitory agents

With respect to working examples supporting enablement, the Examiner admits that Appellants have demonstrated that microinjection of certain compounds directly into cells results in the inhibition of an artificial CREB pathway. In spite of this admission, the Examiner alleges that there is no direct evidence in the application that such result is achieved through inhibition of CREB/CBP binding. Examiner's Answer, page 9, lines 12-16. The Examiner's reliance on this alleged deficiency in proof is unfounded. The present application describes experimental controls which prove that the injected compounds inhibit the specified function via disruption of the CREB/CBP interaction. In this regard, attention is drawn to the specification, page 24, lines 25-33.

> CBP antiserum, pre-incubated with synthetic CBP peptide, was unable to recognize the 265 kD CBP product on a Western blot, and could not inhibit CRE-lacZ reporter activity upon microinjection into NIH3T3 cells. But antiserum treated with an unrelated synthetic peptide (ILS) retained full activity in both Western and microinjection assay, suggesting that the ability of the antiserum to bind CBP was critical for its inhibitory effect on cAMP dependent transcription.

This passage indicates that specificity controls were used to conclude that the antibody binding to CBP in vivo was involved in inhibiting the CREB/CBP interaction that was related to the

biological affect (CRE-LacZ reporter activity). These experiments in the patent application are the foundation of what has become well accepted in the scientific community, that CREB and CBP interact and that such interaction is fundamental to CREB's activity as a transcriptional activator. Appellants point to the Mayr et al. reference, a review article published in 2001, which extensively discusses the CREB/CBP interaction and its implications (e.g. p.599, 604, 605, 606) as evidence of this acceptance of the CREB/CBP interaction. Thus, the Examiner is incorrect that the specification does not demonstrate that inhibitory substances actually disrupt CREB/CBP interaction.

3. The Examiner has failed to properly address the enablement question with respect to the second and third sets of claim groupings

The Examiner has rejected all three groupings of claims with a single argument on the basis that, in each case, the claims are drawn to inhibiting CREB/CBP binding. Examiner's Answer, page 4, lines 5-10. This, however, improperly ignores the purpose to be achieved by each method. This "one size fits all" rejection for enablement attempts to bootstrap the complexities of treating diabetes mellitus with claim groups which are not directed to treatment of a disease per se [i.e., directed to a method of modulating glucose metabolism in an individual (Claims 18-24 and 33) and inhibiting expression of phosphoenolpyruvate carboxykinase (PEPCK) enzyme in an individual (claims 25-32)].

Appellants do not admit that the present claims directed to treating diabetes mellitus are not adequately supported. Rather, the point is that the rejection for enablement rests entirely on

the alleged statements in publications involving diabetes mellitus, which is a different goal from two claim groupings. Modulating glucose metabolism and inhibiting expression of phosphoenolpyruvate carboxykinase (PEPCK) are endpoints with a different narrower goal than treatment of diabetes mellitus. The Examiner's emphasis on the word "may" in the Herzig et al. reference, which Appellents submit must be read out of context to support the rejection, is directed essentially to diabetes mellitus. Thus, the Examiner has failed to properly address the enablement question with respect to claims 18-33.

According, in view of the above it is respectfully submitted that the enablement rejection of all claims should be withdrawn.

Written description rejection

There is no law to support the rejection for written description

The Examiner admits that there is no law on point to support the written description rejection, but asserts that this rejection is consistent with decisions of the Federal Circuit in The Regents of the University of California v. Eli Lilly and Company 119 F.3d 1559, 1568 U.S.P.Q. 2nd 1398, 1406 (Fed. Cir. 1997) and in the University of Rochester v. G.D. Searle & Co. 358 F.3d 916, 969, U.S.P.Q. 2d 1886, 1894 (Fed. Cir. 2004). Examiner's Answer, page 14, lines 1-11.

Appellants respectfully submit that these Federal Circuit decisions do not support the Examiner's proposition that a written description is lacking when different types of compounds

for a method of use are disclosed and the application includes a method (which the Examiner admits is enabled) for identifying additional such compounds. As already discussed in the Appeal Brief, the patent application describes a broad range of inhibitory compounds including the KIX and KID domains and mutated forms of these peptides, specific peptide sequences (see citations to SEQ ID NOS.), the adenovirus E1A oncoprotein, and antibodies.

The evidence supporting enablement in this case is a far cry from the "mere wish or plan for obtaining the claimed chemical invention" which was the situation in Eli Lilly 119 F.3d at 1566 (Fed. Cir. 1997) and from the complete absence of any disclosed inhibitory compounds for the method claims in G.D. Searle & Co. 358 F.3d at 918 (Fed. Cir. 2004). The requirement by the Examiner that there be must be a structure-function relationship shown for the genus of inhibitory compounds for written description to be present (Examiner's Answer, p.14) goes well beyond these decisions and the settled law.

Accordingly, in view of the above it is respectfully submitted that the written description rejection of all claims should be withdrawn.

Conclusion

For the reasons discussed above, Appellants believe the instant claims are in condition for allowance, and Appellants respectfully request that the rejections be withdrawn or reversed.

PATENT
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Respectfully submitted,

Date: October 11, 2004

By _____

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